SYNTHESIS OF SOME NOVEL N, S-CONTAINING HETEROCYCLES AND THEIR BIOLOGICAL ACTIVITIES

Synopsis of the Ph.D. Thesis to be submitted

To

MANGALORE UNIVERSITY

For the award of the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

By

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Synopsis of the Ph.D. thesis to be submitted to Mangalore University for the award of the degree of Doctor of Philosophy in Chemistry

Title of the Thesis:	Synthesis of some novel N,S-containing heterocycles and their biological activities
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Chapter 1: A brief review on the chemistry of triazoles.

Azoles are a class of five-membered heterocycles, with a nitrogen atom and at least one other non-carbon atom.They found widely in natural sources and several drugs. Their action on mycotic biochemistry and physiology has been studied extensively. Triazoles are five membered heterocycles containing three nitrogen atoms. According to the position of nitrogen atoms the triazoles can exist in two isomeric forms namely 1,2,3-triazole and 1,2,4-triazole. These triazoles show various medicinal properties such as antimicrobial,anti-inflammatory,anticonvulsant,antitubercular etc [1-4].

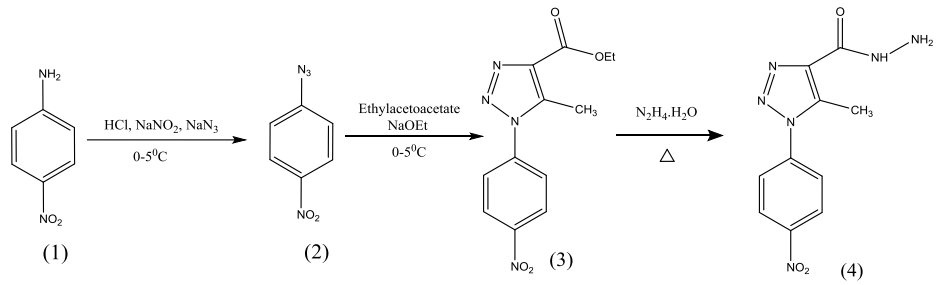
Triazoles find numerous applications in industry, namely as dyestuffs, fluorescent whiteners, photostabilizers, optical brightening agents and as corrosion inhibitors [5-7]. Beyond this, these compounds are extensively studied by many research groups due to their theoretical interest and synthetic usefulness.

So a brief review of literature related to biologically active triazoles,reported in the literature upto August 2020 is given in this chapter.

Impelled by the literature reports,it was planned to synthesize a novel series of heterocycles carrying triazole and to screen the compounds for their pharmacological potency.

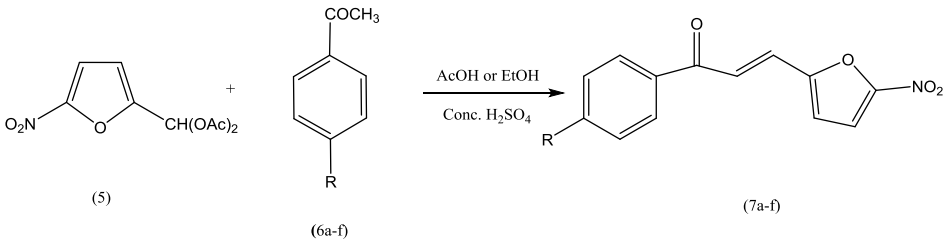
Chapter 2: Antioxidant and antimicrobial activity of new triazole linked pyrazoline hybrid compounds.

This chapter deals with synthesis, characterization, antioxidant and antimicrobial activity of (5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl-(3-aryl)-5-phenyl-2,3-dihydro-1H-pyrazol-1-yl)methanone derivatives. The ethyl-5-methyl-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate **(3)** was prepared by the reaction of 1-azido-4-nitrobenzene **(2)** with ethylacetoacetate in the presence of sodium ethoxide. The 1-azido-4-nitrobenzene was in turn obtained by the diazotization of p-nitroaniline **(1)** followed by the reaction with sodium azide. The 5-methyl-1-(p-nitrophenyl)-1H-1,2,3-triazole-4-carbohydrazide **(4)** was obtained in good yield by hydrazinolysis of ethyl-5-methyl-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate **(3)**[8].

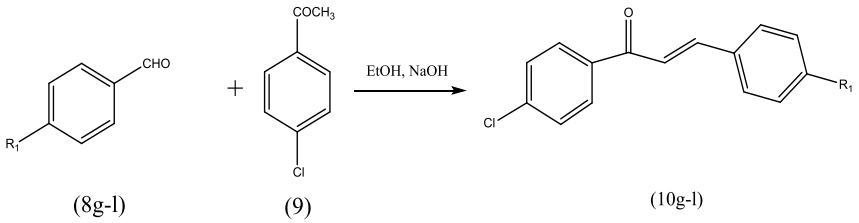


Scheme I: Synthesis of 5-methyl-1-(p-nitrophenyl)-1H-1,2,3-triazole-4-carbohydrazide

1-Aryl-3-(5-nitro-2-furyl)-2-propen-1-ones/ 1,3-Diaryl prop-2-en-1-ones**(7a-f/10g-*l*)** were synthesized through Claisen-Schmidt condensation reaction of 5-nitro-2-furfural diacetate/ substituted aldehyde with substituted acetophenones[9].

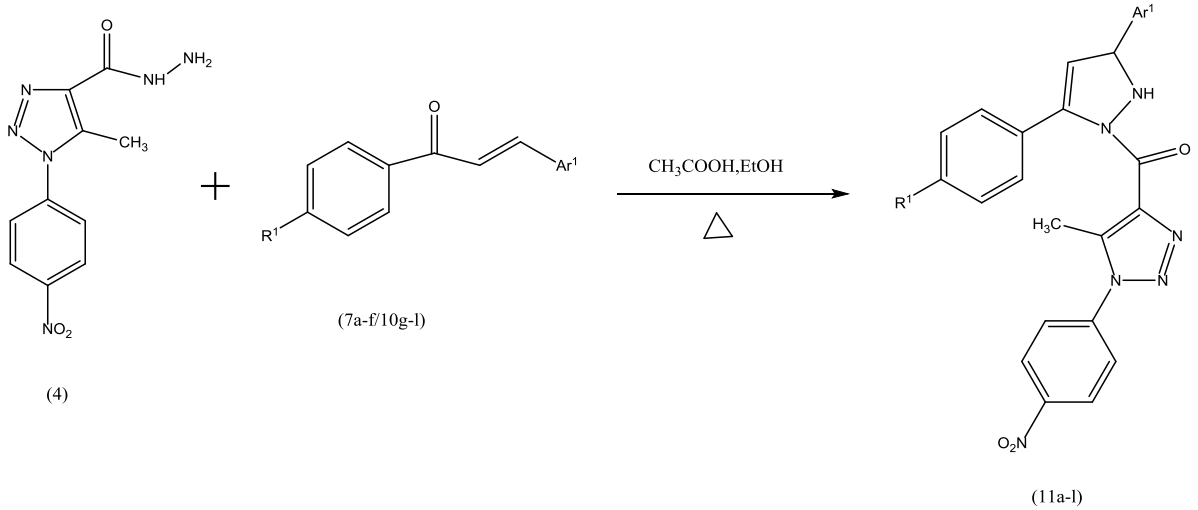


Scheme II: Synthesis of 1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones derivatives



Scheme III: Synthesis of 1,3-Diaryl prop-2-en-1-ones

The α, β-unsaturated ketones were when treated with triazole hydrazide **(4)** in the presence of acetic acid gave (5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl-(3-aryl)-5-phenyl-2,3-dihydro-1H-pyrazol-1-yl)methanone derivatives**(11a-*l*)**.

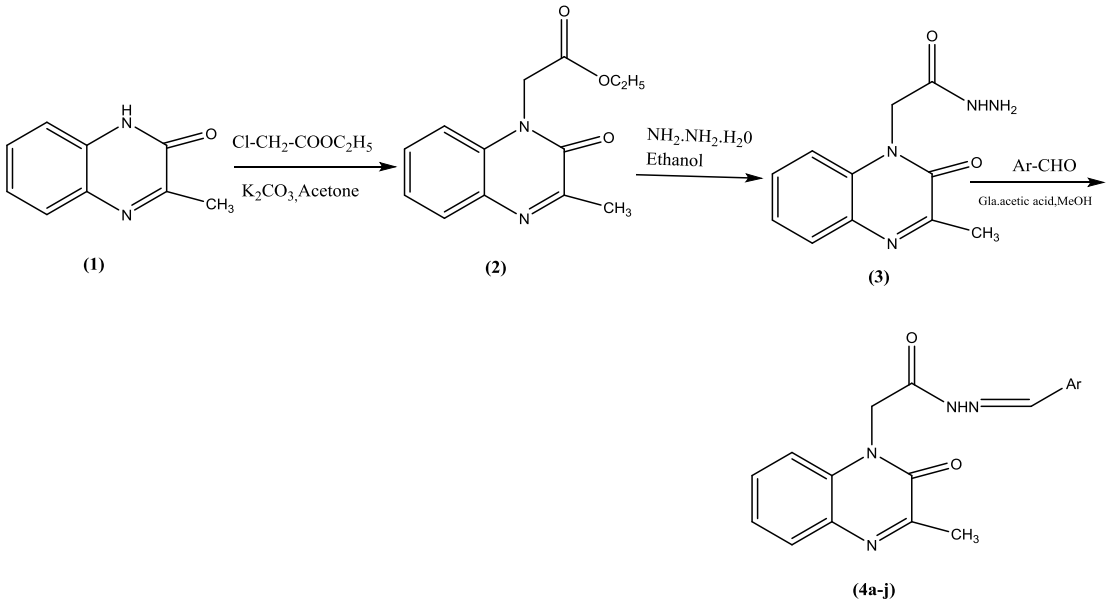


Scheme IV : Synthesis of (5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl-(3-(5-nitrofuran-2-yl)-5-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl)methanone derivatives.

The new compounds were screened for their antimicrobial and antioxidant property.

Chapter 3: Synthesis,Characterization and biological evaluation of hydrazones.

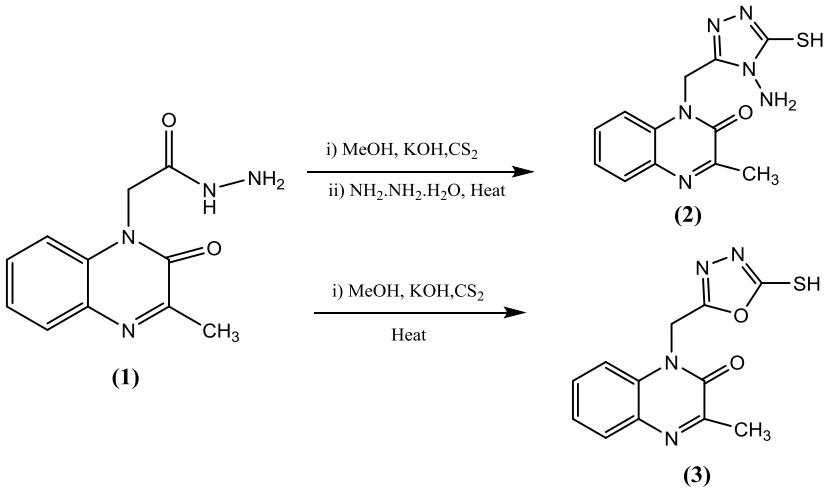
This chapter deals with the synthesis of 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-N'-[(Substituted aryl)methylene]acethydrazone and evaluation of their antioxidant activity.The required starting material, 3-methylquinoxalin-2(1*H*)-one **(1)** was prepared in good yield by condensation of *o*-phenylenediamine and pyruvic acid. The reaction of **(1)** with ethyl chloroacetate, in the presence of potassium carbonate yielded ethyl-(3- methyl-2-oxo-quinoxalin-1(2*H*)-yl) acetate **(2)**, which on reaction with hydrazine hydrate in methanol gave 2-(3-methyl-2-oxo-quinoxalin-1(2*H*)-yl)acethydrazide **(3)**. Condensation of **(3)** with substituted aldehydes in Glacial acetic acid medium gave the respective 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-N'-[(Substituted aryl)methylene]acethydrazones **(4a-j)** [10-11] .The newly synthesized compounds were characterized by FT-IR,^{1}H NMR and mass spectra. The new compounds are also evaluated for their antioxidant and antibacterial property.



Scheme I: Synthesis of 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-N'-[(Substituted aryl)methylene]acetohydrazone derivatives.

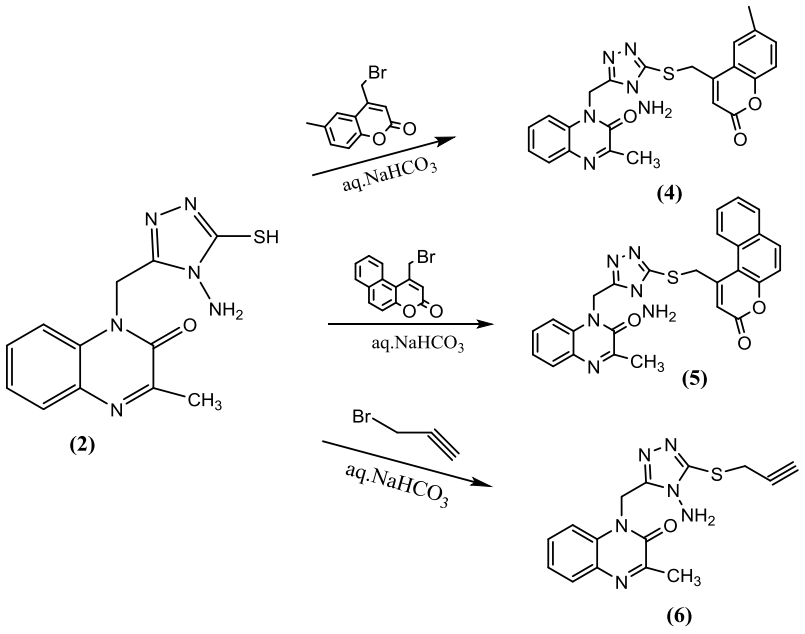
Chapter 4: Synthesis, Characterization and biological evaluation of triazole containing quinoxaline derivatives.

In this chapter S-alkylation of 1-[(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl]-3-methylquinoxalin-2(1*H*)-one/ 1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]]-3-methylquinoxalin-2(1*H*)-one and 1,3-dipolar cycloadditon reaction of aryl azides with 1,2,4-triazole/1,3,4-oxadiazole substituted terminal alkynes was studied. The terminal alkynes containing 1,2,4-triazole and 1,3,4-oxadiazoles were prepared by multistep reaction. Quinoxalin acethydrazide **(1)** on reaction with CS_2,KOH and hydrazine hydrate/ CS_2,KOH gave corresponding1-[(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-3-methylquinoxalin-2(1*H*)-one **(2)** /1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-3-methylquinoxalin-2(1*H*)-one **(3)**.

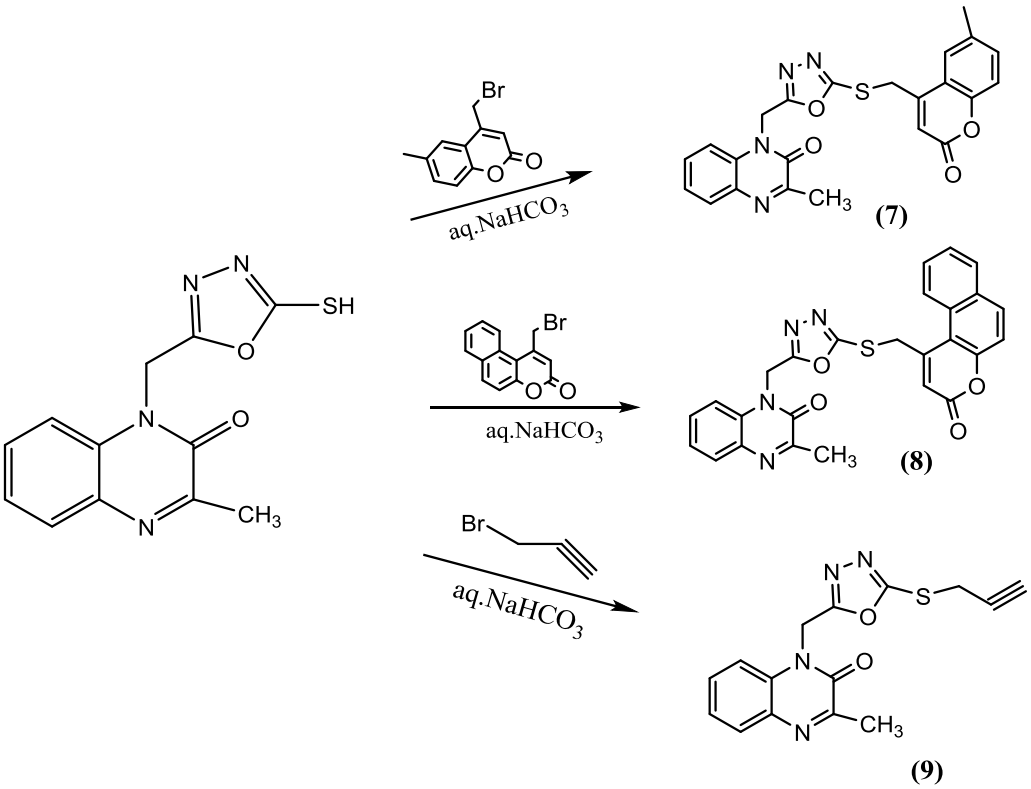


Scheme I: Synthesis of 1-((4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl)-3-methylquinoxalin-2(1*H*)-one **(2)** and 1-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-3-methylquinoxalin-2(1H)-one **(3)**.

The 1,2,4-triazole/1,3,4-oxadiazole thiols (**2/3**) were treated with propargyl bromide/4-(bromomethyl)-6-methyl-2*H*-chromen-2-one/1-(bromomethyl)-3H-benzo[*f*]chromen-3-one in presence of a strong base at room temperature to give corresponding S-alkylated product **(4-9)**

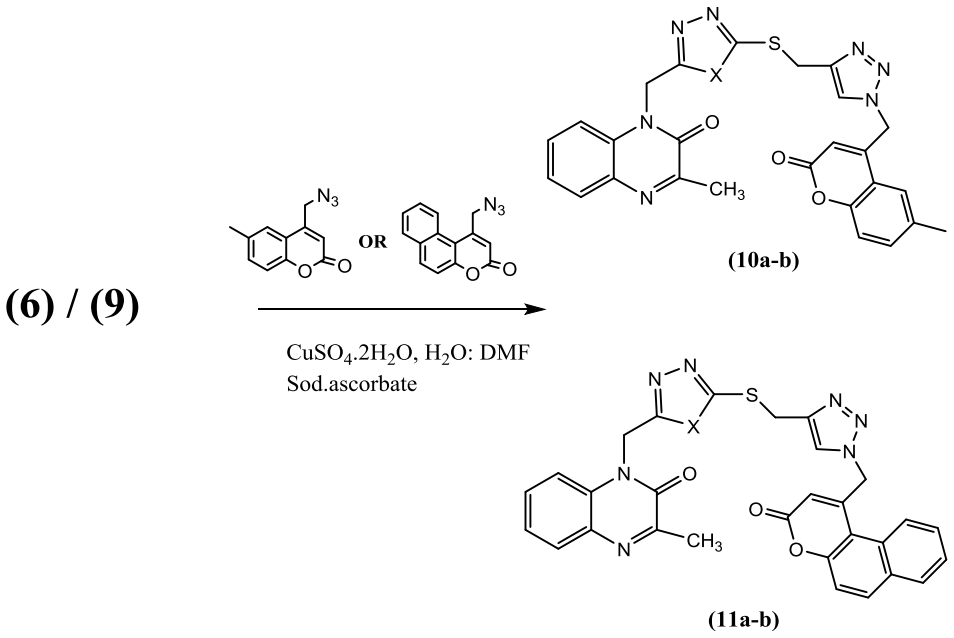


Scheme II: Synthesis of 1-[(4-amino-5-(((substituted) methyl) thio)-4*H*-1,2,4-triazol-3-yl)methyl]-3-methylquinoxalin-2(1*H*)-one derivatives.



Scheme III: Synthesis of 3-methyl-1-[(5-(((substituted)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2(1*H*)-one derivatives.

The terminal alkynes **(6/9)** and aryl azide were subjected to 1,3-dipolar cycloaddition reaction in presence of Cu(I) catalyst [12] and gave 1-[(4-amino-5-(((1-((substituted)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-4*H*-1,2,4-triazol/1,3,4-oxadiazol-3/2-yl)methyl]-3-methylquinoxalin-2(1*H*)-one derivatives **(10)/(11)**. The newly synthesized compounds were characterized by FT-IR, ^{1}H NMR and mass spectra. The new compounds are also evaluated for their ant-ioxidant and anti-bacterial property.

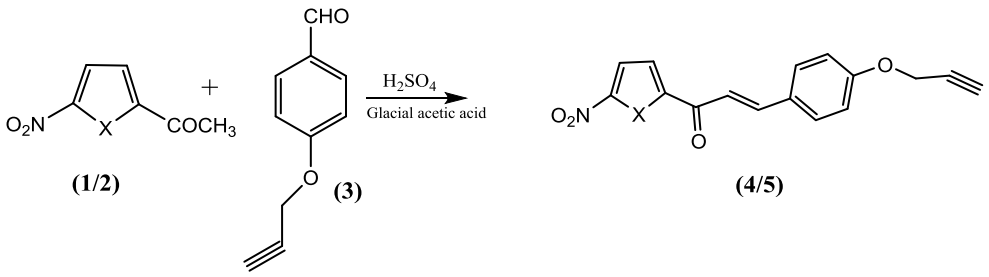


Scheme IV: Synthesis of 1-[(4-amino-5-(((1-((substituted)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-4*H*-1,2,4-triazol/1,3,4-oxadiazol-3/2-yl)methyl]-3-methylquinoxalin-2(1*H*)-one derivatives.

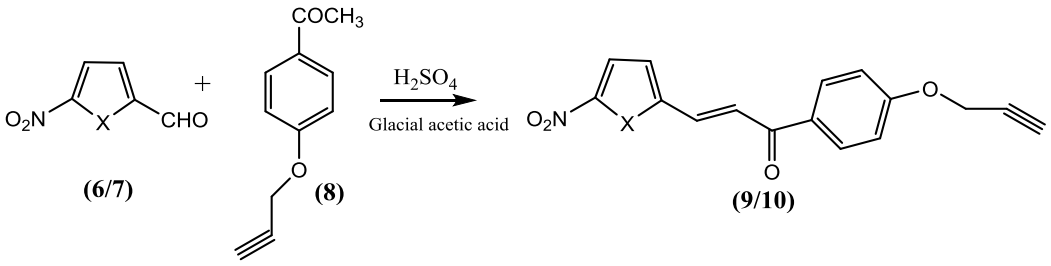
Chapter 5a: Synthesis, Characterization and corrosion studies of Chalcone derivatives.

In this chapter, four new 1/3-(5-nitro(furan/thiophen)-2-yl)-3/1-(4-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one derivatives were synthesized by Claisen-Schmidt condensation reaction. The reaction scheme for the synthesis of chalcone derivatives are presented in **Scheme I** and **II**.

4-Hydroxybenzaldehyde/acetophenone was treated with propargyl bromide in the presence of anhydrous potassium carbonate in DMF to yield 4-O-propargylated benzaldehyde/acetophenone **(3/8)**, this when reacted with appropriately substituted acetophenones/aldehydes **(1/2 and 6/7)** in the presence of sulphuric acid gave the corresponding chalcone derivatives [13] **(4/5 and 9/10)**.



Scheme I: Synthesis of 1-(5-nitrofuran/thiophen-2-yl)-3-(4-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one .

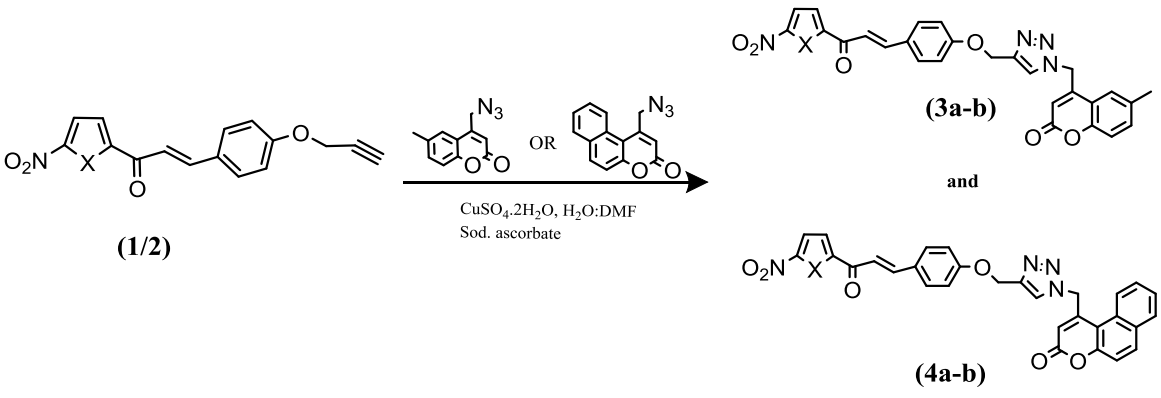


Scheme II: Synthesis of 3-(5-nitrothiophen/thiophen-2-yl)-1-(4-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one

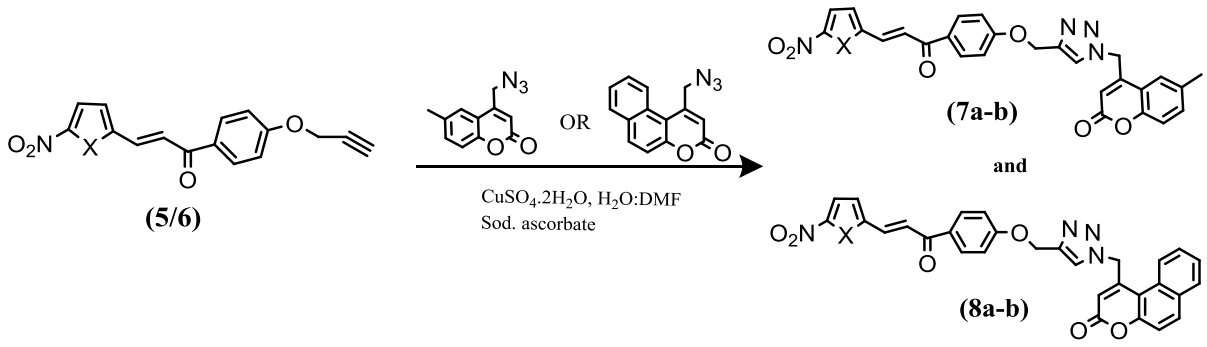
Corrosion inhibition property of 1-(4-nitrothiophen-2-yl)-3-(4-((prop-2-yn-1-yl)oxy)phenyl)prop-2-en-1-one on 6063 Al alloy in 0.5M HCl were studied using weight loss, potentiodynamic polarization and electrochemical impedance spectroscopy (EIS) method .

Chapter 5b: Synthesis, Characterization and Biological evaluation of Chalcone containing triazole derivatives.

In this chapter 1,3-dipolar cycloaddition reaction of aryl azides with chalcone containing terminal alkynes were studied under Cu(I) catalyst,employing sodium ascorbate . 4-Azidomethyl coumarins/chromenes were synthesized from corresponding bromo methyl coumarins in the presence of sodium azide and acetone. The chalcone containing terminal alkynes **(1-4)** and aryl azides when subjected to 1,3-dipolar cycloaddition gave the corresponding triazole derivatives [12].The new compounds were characterized by FT-IR, ^{1}H NMR and mass spectroscopy.



Scheme I: Synthesis of 4-[(4-((4-(3-(5-nitrofuran/thiophen-2-yl)-3-oxoprop-1-en-1-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl]-substituted derivatives.



Scheme II: Synthesis of 4-[(4-((4-(3-(5-nitrofuran/thiophen-2-yl)acryloyl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl]-substituted derivatives.

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Publications

List of Research papers published / Communicated in journals

1. Antioxidant and Antimicrobial activities of new Triazole–linked Pyrazoline hybrid compounds.
   Aparna.K, Balakrishna Kalluraya ,B.C.Revanasiddappa,Mr.Srinivas Hebbar, *J. Appl. Chem.*,**8**(6),2440 (2019).
2. Electrochemical and quantum chemical studies of 1-(4-nitrothiophen-2-yl)-3-(4-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one on the corrosion inhibition of 6063al in hydrochloric acid
   Aparna.K, Balakrishna Kalluraya ,Raviprabha K, *J.Appl.Chem.*,**9**(5),2020
3. Synthesis and biological activity of some new triazolylbenzodiazepines.
   Balakrishna Kalluraya, Sahana Mallya, Asma,**Aparna K**, B.R Kaushik, *Indian J. Heterocycl. Chem.*,**26**(3&4),121 (2016).
4. Synthesis, Characterization and Biological Activities of 1,2,3-Triazole Containing Substituted Cyclohexanones.
   Balakrishna Kalluraya, Sushma K, Anish Kumar K, B.R Kaushik, **Aparna K,** Vignesh Shetty, *J. Appl. Chem.*,**6**(1),8 (2017).
5. Microwave assisted synthesis and biological studies of thiazoles, thiazolones containing quinoline and tetrazole moiety.
   B. Kalluraya, H.S. Vidyashree Jois, Asma, **K.Aparna**, N. Bhagya and K.R. Chandrashekar, *Indian J. Heterocycl. Chem.*,**27**(4),443 (2017).

List of papers presented in conferences / attended webinars.

1. Microwave assisted synthesis of sydnone containing 2,5-disubstituted 1,3,4-thiadiazines under solvent free condition **(PP). Aparna K,** B.Kalluraya, Presented in 35th annual national conference of Indian council of chemists, held at Haribhai V Desai college, pune during 22nd-24th December 2016.
2. Synthesis of novel triazole –linked pyrazoline hybrid compounds **(PP)**. **Aparna K,** B.Kalluraya, Presented at National Conference on Science and Technology – Reaching the Unreached –Recent advances in Physical,Mathematical,Chemical

and Biological Sciences for Energy, Health and Environment, held at Mangalore University,Mangalagangothri during 8-9th September 2017.

3. Synthesis and antioxidant activity of quinoxaline derivatives **(OP).** Presented in 37th annual national conference of Indian council of chemists, held at NITK Surathkal,Mangalore during 12th -14th December 2018.
4. Attended a webinar on "Basics of electron microscopy" organized by Jyothi Institute of Technology,Bangalore, held on 8th August 2020.
5. Attended a webinar on "Importance, Necessity and Thrust Areas of Research-an Indian Scenario" organized by Reva University Bangalore, held on 8th August 2020.
6. Attended a webinar on "NMR:Theory,Instrumentation and Application" organized by Srinivasa Ramanujan Institute of Basic Sciences,Kottayam, held on 20-23rd August 2020.

Aparna K — Prof.B.Kalluraya

(Research Scholar) — (Research Guide)